contain a heterologous antibiotic resistance gene, the cell obtained by treating brain capillary vessels of a transgenic animal into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced with protease and subculturing the resulting cells at 33°C.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i - iv).

REMARKS

Claims 1-14 are currently pending in the application. Claims 1, 3, 5-7, 9-11 and 13-14 are amended to specify that the cell is "capable of growing at 33 °C," rather than is "immortal at conditions below 39 °C." Support for this amendment is found throughout the specification (see, e.g., page 18, line 4-5; page 15, lines 5-7; page 16, lines 2-4 and 11-13; and page 17, lines 16-18). No new matter is added. Thus, the present amendments do not necessitate new grounds for search or examination.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action states that the specification lacks support for a cell that "does not contain a heterologous antibiotic resistance gene." Applicants respectfully traverse this rejection.

In essence, the Examiner is objecting to the inclusion of a negative limitation, wherein the cell *does not* contain a specific marker gene, because there is no explicit support in the specification for this negative limitation. As an initial matter, there is no per se rule against negative limitations, provided they do not introduce issues of indefiniteness, undue breadth, or

obviousness (*In re Hawkins*, 179 U.S.P.Q. 163 (C.C.P.A. 1973), which is not the case here. In the present case, the amendment simply makes explicit what is inherent in the specification. Because the amendment does not correct any fundamental defect in the original disclosure, it should be allowed for the purpose of clarity.

Regarding *support* in the specification for the newly added negative limitation (**absence of a heterologous antibiotic resistance gene**), the present case is analogous to the situation presented in *Ex parte Parks*, 30 U.S.P.Q.2d 1234 (Bd. Pat. App. & Int'f 1993). In *Parks*, the claim was to a chemical process requiring decomposition of a sample; the added phrase was that the decomposition be conducted "**in the absence of a catalyst**." The examiner had rejected the amended claim because **the specification did not literally refer to absence of a catalyst**. However, the Board reversed the rejection, stating that "[t]hroughout the discussion [of the process] which would seem to cry out for a catalyst if one were used, no mention is made of a catalyst" (Id. at 1236). Similarly, in the instant case, the specification does not literally refer to the absence of a heterologous antibiotic resistance gene. No mention is made in the application, including the examples, of a cell containing such a marker. As in the *Parks* case, the present disclosure would seem to "cry out for [a marker] if one were used." Applicants clearly teach how to make the claimed cells; however, nowhere do they teach how to make a cell containing a heterologous antibiotic resistance gene. In fact, the presence of such a gene would significantly affect the properties of the Applicants' immortalized cells, making them unsuitable for subsequent transformations and selection of transformed cells using a neomycin resistance gene as a selective marker. Had Applicants intended to modify their cells in this way, they clearly would have stated so in the application.

Applicants respectfully submit that specification provides support for the limitation that the cells "do not contain a heterologous antibiotic resistance gene," and respectfully request that the rejection on this basis be reconsidered and withdrawn.

Withdrawn Rejection Under 35 U.S.C. § 102(b)

The rejection of claims 1, 3, 6, 11 and 14 under 35 U.S.C. § 102(b) as being anticipated by Greenwood et al. (*J. Neuroimmunol.* 71:51-63. 1996) was **withdrawn** in the final Office Action. The Office Action states that "cells comprising the claim limitations and that do not comprise a heterologous antibiotic resistance gene are not anticipated by the prior art" and "the patentability of claims are accepted and acknowledged" (Final Office Action, page 3, last paragraph).

Although the limitation regarding the absence of a heterologous antibiotic resistance gene clearly overcomes this rejection, as acknowledged by the Examiner, and is supported by the original disclosure, as discussed above, Applicants have amended the claims to further distinguish their invention from the cited reference. Applicants note the Examiner's statement that "the limitation that the cells are immortal at conditions below 39 °C . . . does not distinguish the claimed invention from the teachings of Greenwood et al. because . . . the Greenwood et al. cells grow at 37 °C, which meets the limitation of below 39 °C" (Final Office Action, page 4, lines 1-4). Again, although Applicants do not acquiesce to the Examiner's rejections, and although the limitation regarding the absence of a heterologous antibiotic resistance gene overcomes the prior art rejections, Applicants have amended the claims to replace the phrase "immortal at conditions below 39 °C" with "capable of growing at 33 °C." Although the Greenwood et al. cells grow at 37 °C, unlike Applicants' cells, they are not capable of growing at 33 °C.

Withdrawn Rejection Under 35 U.S.C. § 103

The rejection of claims 1-3, 6-7, 10-11 and 14 under 35 U.S.C. § 103 as being unpatentable in view of Rudland *et al.* (International Application WO 97/39117, 1997) and Greenwood *et al.* (U.S. Pat. No. 6,090,624, 2000), and further in view of Roux *et al.* (*J. Cell. Physiol.* 159:101-113, 1994) and Villalobous *et al.* (*J. Pharmacol. Exp. Ther.* 282:1109-1116, 1997) has been **withdrawn** in the final Office Action. The Office Action states that "the

patentability of cells comprising the claim limitations and that do not comprise a heterologous antibiotic resistance gene is accepted and acknowledged" (page 4, second paragraph).

Although the limitation regarding the absence of a heterologous antibiotic resistance gene clearly overcomes this rejection, as acknowledged by the Examiner, and is supported by the original disclosure, Applicants have amended the claims to further distinguish their invention, as discussed above. Again, although Applicants do not acquiesce to the Examiner's rejections, and although the limitation regarding the absence of a heterologous antibiotic resistance gene overcomes the rejection under Section 103, Applicants have amended the claims to replace the phrase "immortal at conditions below 39 °C" with "capable of growing at 33 °C." Although the cells described in the cited references may grow at 37 °C, unlike Applicants' cells, they are not capable of growing at 33 °C.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDMENTS:

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Please amend claims 1, 3, 5-7, 9-11 and 13-14 as follows:

1. (Thrice Amended) A conditionally immortalized cell established from a transgenic animal into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced, and wherein the cell exhibits an inside-outside polarity when cultured in vitro, and is capable of taking up a drug, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene.

3. (Thrice Amended) An established cell derived from retinal capillary endothelial cells, which expresses a temperature sensitive SV40 large T-antigen gene, GLUT-1 transporter, and p-glyoprotein, and wherein the cell exhibits an inside-outside polarity when cultured in vitro, and is capable of taking up a drug, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene.

5. (Thrice Amended) A method of establishing a conditionally immortalized cell which expresses a temperature sensitive SV40 large T-antigen gene, GLUT-1 transporter, and p-glycoprotein, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene, the method comprising treating retinal capillary vessels of a transgenic animal into which a large T-antigen gene of

SV40 temperature sensitive mutant tsA58 has been introduced with protease and subculturing the resulting cells at 33°C.

6. (Thrice Amended) An established cell which expresses a temperature sensitive SV40 large T-antigen gene, GLUT-1 transporter, and p-glycoprotein, and wherein the cell exhibits an inside-outside polarity when cultured in vitro, and is capable of taking up a drug, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene, the cell obtained by treating retinal capillary vessels of a transgenic animal into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced with protease and subculturing the resulting cells at 33°C.

7. (Thrice Amended) An established cell derived from choroid plexus epithelial cells, wherein the cell exhibits an inside-outside polarity when cultured in vitro, and is capable of taking up a drug, which expresses a temperature sensitive SV40 large T-antigen gene, shows localization of Na^+-K^+ ATPase and GLUT-1 transporter in the cell membrane, and when cultured in a monolayer, shows the localization of Na^+-K^+ ATPase in the apical side, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene.

9. (Thrice Amended) A method of establishing a conditionally immortalized cell which expresses a temperature sensitive SV40 large T-antigen gene, shows localization of Na^+-K^+ ATPase and GLUT-1 transporter in the cell membrane, and when cultured in a monolayer, shows the localization of Na^+-K^+ ATPase in the apical side, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous

antibiotic resistance gene, the method comprising treating choroidal epithelium tissues of a transgenic animal into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced with protease and subculturing the resulting cells at 33°C.

10. (Thrice Amended) An established cell which expresses a temperature sensitive SV40 large T-antigen gene, wherein the cell exhibits an inside-outside polarity when cultured in vitro, and is capable of taking up a drug, and shows localization of Na^+-K^+ ATPase and GLUT-1 transporter in the cell membrane, and when cultured in a monolayer, shows the localization of Na^+-K^+ ATPase in the apical side, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene, which is obtained by treating choroidal epithelium tissues of a transgenic animal into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced with protease and subculturing the resulting cells at 33°C.

11. (Thrice Amended) An established cell derived from brain capillary endothelial cells, wherein the cell exhibits an inside-outside polarity when cultured in vitro, and is capable of taking up a drug, which expresses a temperature sensitive SV40 large T-antigen, GLUT-1 transporter, p-glycoprotein, alkaline photosphatase, and γ- glutamyltransferase, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene.

13. (Thrice Amended) A method of establishing a conditionally immortalized cell which expresses a temperature sensitive SV40 large T-antigen gene, GLUT-1 transporter, p-glycoprotein, alkaline phosphatase, and γ-glutamyltransferase,

[and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene, the method comprising treating brain capillary vessels of a transgenic animal into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced with protease and subculturing the resulting cells at 33°C.

14. (Thrice Amended) An established cell which expresses a temperature sensitive SV40 large T-antigen gene, GLUT-1 transporter, p-glycoprotein, alkaline phosphatase and γ-glutamyltransferase, and wherein the cell exhibits an inside-outside polarity when cultured in vitro, and is capable of taking up a drug, [and] wherein the cell is capable of growing at 33 °C [immortal at conditions below 39°C], and wherein the cell does not contain a heterologous antibiotic resistance gene, the cell obtained by treating brain capillary vessels of a transgenic animal into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced with protease and subculturing the resulting cells at 33°C.